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Rapid onset of bronchodilation in COPD: a placebo-controlled study comparing formoterol (Foradil® Aerolizer™) with salbutamol (Ventodisk™)

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Abstract Formoterol fumarate is a β_2-agonist bronchodilator that combines a fast onset of action with a long duration of action. Its fast onset of action is well documented in asthma but has not been directly compared with that of salbutamol in patients with chronic obstructive pulmonary disease (COPD). This randomized, double-blind, placebo-controlled study was conducted to assess the bronchodilatory effects over the first 3 h after inhalation of single doses of formoterol 24 μg delivered via the Aerolizer™ dry powder inhaler device (double-blind), or salbutamol 400 μg delivered via Diskhaler® dry powder inhaler (single-blind) in patients with COPD. A total of 24 patients with COPD were randomized [mean age 61·6 ± 7·8 years, mean forced expiratory volume in 1 sec (FEV_1) 1·38 ± 0·32 l and 45·8 ± 9·6% of predicted]. Inhalation of formoterol or salbutamol resulted in similar increases in FEV_1 from 0 to 3 h post-dose. Both drugs produced similar bronchodilation by 5 min, which became almost maximal by 30 min. The primary efficacy variable, the area under the curve (AUC) of the FEV_1 increase above predose baseline from 0 to 30 min ($AUC_{0-30\ min}$), demonstrated significant effects for formoterol (mean 5·89 ± 4·67 l min^{-1}), and salbutamol (mean 6·06 ± 4·34 l min^{-1}), which were not statistically different from each other but statistically significantly higher ($P < 0·0001$) than that observed with placebo (−0·32 ± 2·59 l min^{-1}). In addition, both formoterol and salbutamol produced similar and rapid increases in forced vital capacity (FVC). In summary, this study confirms the rapid onset of action of formoterol and indicates that the onset of action of formoterol and salbutamol are similar in patients with COPD.

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INTRODUCTION

Formoterol (Foradil®) is a unique β_2-agonist that combines the clinical benefits of a long duration of action with a rapid onset of action (1). In a placebo-controlled trial with formoterol delivered via the Aerolizer™ dry powder inhaler, Maesen *et al.* (2) were able to show that patients' subjective perception of the onset of bronchodilation matched objective clinical measurement of the onset of bronchodilation. In addition, in comparative clinical trials in patients with moderately severe asthma, formoterol has been shown to have a similar onset of action to salbutamol producing significant bronchodilation within 1 min after inhalation (3–5). Not only is fast onset of action important for patient re-assurance of prompt symptom relief, it could also be a key factor in patient compliance; if symptom relief is experienced rapidly after dosing, the patient feels that the treatment is effective and will continue with it.

Chronic obstructive lung disease (COPD) differs from asthma in that it is a chronic progressive condition that requires regular long-term treatment once the individual has progressed beyond the initial stages of the disease (6). This treatment is maintained at the same level or increased as needed; there is no step-down therapy. Bronchodilators are central to the symptomatic treatment of COPD and whilst the short acting β_2-agonists are regularly prescribed the benefits they offer in COPD when used frequently in COPD are not clear. The benefits of longer-acting bronchodilators over regular use of short-acting bronchodilators is becoming more clear with the publication of new data that suggest that early intervention with formoterol may be a useful strategy for some patients with COPD (7,8). Clinical trials in

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COPD have shown formoterol to be an effective bronchodilator in patients who have differing degrees of forced expiratory volume in 1 sec (FEV_1) reversibility (both $\geq$15% and $<$15% of the baseline value) (9,10). It provides significantly greater bronchodilation than ipratropium (7), with a sustained improvement in lung function that is superior to theophylline (8,11). The onset of action of formoterol in COPD has been shown to be faster than that of ipratropium (12) but has not been directly compared with that of salbutamol.

The purpose of this current study was to compare the onset of action of formoterol in COPD with salbutamol, in order to define further the potential role of formoterol in COPD. The primary objective was to assess the bronchodilatory effects of formoterol and salbutamol compared with placebo in terms of the FEV_1 area under the curve from 0 to 30 min ($AUC_{0-30\,min}$) following single-dose administration. Secondary objectives were to compare the bronchodilatory effects of these two drugs with placebo with respect to other efficacy variables during 3 h following a single dose.

METHODS

Study design

The study was designed as a randomized, placebo-controlled, double-blind for formoterol and placebo, single-blind for salbutamol, three-way, cross-over trial. Salbutamol reversibility testing was performed during a 7-day screening phase, which was followed by randomization at the start of the main trial. The three-way cross-over design allowed intermittent comparisons and a double-blind (for formoterol and placebo); single-blind (for salbutamol) design was used to minimize bias. Double-blind treatment with salbutamol was not possible owing to the unavailability of placebo matched to salbutamol.

Study population

A total of 40 patients were screened and 25 were randomized. All patients were between the ages of 40–75 years with stable COPD according to inclusion criteria. Patients were selected on the basis of a history of smoking of $>$20 pack-years, who met the following criteria: (a) a diagnosis of COPD based on the American Thoracic Society guidelines (13); (b) FEV_1 of between 30% and 60% of the predicted value and at least 1000 ml after at least 6 h wash-out from short-acting bronchodilators, with FEV_1/FVC $<$88% of predicted in men or 89% of predicted in women; (c) demonstrable intermediate reversibility with an increase in FEV_1 of 200 ml maximum and 5–15% over baseline within 30 min of 400 μg salbutamol ($2 \times 200\,\mu$g Ventodisk^{TM}). Exclusion criteria included all patients with a significant medical condition and those who had been hospitalized for an acute exacerbation of COPD within 1 month prior to the start of the study. Patients using non-potassium-sparing diuretics, β-blocking agents, quinidine or quinidine-like medications (anti-arrhythmics), tricyclic anti-depressants, selective serotonin re-uptake inhibitors and monoamine oxidase inhibitors were also excluded from the trial.

Use of oral corticosteroids, theophylline or other xanthine derivatives, oral or inhaled anti-cholinergics, oral or inhaled long-acting β_2-agonists, or inhaled short-acting β_2-agonists were not allowed during the main study period.

Treatments

Treatments consisted of a single dose of each trial medication administered as follows: formoterol 24 μg, given as two dry powder capsules each containing 12 μg of formoterol via Aerolizer^{TM} (Novartis Pharma AG, Basel, Switzerland); placebo, matched to formoterol dry powder capsules via Aerolizer^{TM} (Novartis Pharma AG); salbutamol 400 μg, two puffs of dry powder (Ventodisk^{TM} 200 μg) via Diskhaler^{TM}, 200 μg per puff (Glaxo Wellcome, France).

Treatment with inhaled or nasal corticosteroids and rescue medication with salbutamol between visits was allowed during the trial.

Efficacy assessments

The primary efficacy parameter was $AUC_{0-30\,min}$ of FEV_1 in $l\,min^{-1}$. Secondary efficacy parameters included: $AUC_{0-1\,h}$ of FEV_1 ($l\,min^{-1}$), $AUC_{0-3\,h}$ of FEV_1 ($l\,min^{-1}$), maximal change in FEV_1 as a percentage of predicted value, maximal change in FEV_1 in litres, and maximal change from predose in forced vital capacity (FVC) in litres.

Other spirometric measurements included FEV_1 and FVC, measured during screening (qualifying value for reversibility), and before dosing and 5, 10, 15 and 30 min, 1 h, 2 h, 3 h and 4 h after dosing at during the main trial. Spirometry had to be performed within $\pm$1 min of the scheduled 5-min time point and within $\pm$5 min of the scheduled 15-min, 30-min, 1-h, 2-h, 3-h and 4-h time points.

Safety assessments

All adverse events were recorded and vital signs including pulse rate and blood pressure were measured after 5 min rest at each visit.

Statistical methods

The primary efficacy variable was the $AUC_{0-30\,min}$ of FEV_1 ($l\,min^{-1}$), calculated from repeated measurements of FEV_1, predose and 5 min, 10 min, 15 min, 30 min after study drug intake at each visit. Absolute level of FEV_1 (l)

was used in this calculation. An analysis of variance model including sequence, treatment, visit and patient (random) as factors was used for analysis.

Pairwise comparisons between treatment means were based on t-tests using the pooled error term of the model. The main comparison of interest being that of formoterol with placebo, no adjustment for multiple comparisons was made.

AUC_{0-1h} ($l\,min^{-1}$) and AUC_{0-3h} ($l\,min^{-1}$), maximal change in FEV_1 (expressed in litres, in percentage of baseline value and as a percentage of the predicted value), and maximal change in FVC (l), were analysed in the same way as the primary efficacy variable. All analyses were carried out on the 'intent-to-treat' (ITT) population.

RESULTS

Baseline demographics and background characteristics

A total of 40 patients were screened, of whom 25 were randomized. Of the 15 patients discontinued prior to randomization, 14 failed to fulfil selection criteria and one withdrew consent. One patient was included twice in the study because of incomplete efficacy data due to a spirometer breakdown during the last assessment—he received the same treatment sequence twice. The ITT population consisted of 24 patients (83·3% males and 16·7% females). Background characteristics and baseline spirometry are presented in Table 1.

Table 1. Baseline demographics and background characteristics. ITT population

Parameter	*n* (%)	Mean ± SD
Number of patients	24	
Male	20 (83·3%)	
Female	4 (16·7%)	
Age (years)		61·6 ± 7·8
Duration of COPD (years)		11·9 ± 7·8
Smoking history (pack-years)		48·0 ± 17·36
Current smokers	11 (45·8%)	
Previous smokers	13 (54·2%)	
Lung function		
Baseline FEV_1 (l)		1·38 ± 0·32
FEV_1/FVC (%)		54·3 ± 8·3
FEV_1 as % of predicted		45·8 ± 9·6
FEV_1 reversibility (l)		0·18 ± 0·07
FEV_1 reversibility (%)		13·5 ± 4·8

SD=standard deviation.

Efficacy results

Formoterol and salbutamol produced statistically similar (P=0·85) increases in FEV_1 $AUC_{0-30\,min}$ from baseline: formoterol 5·89 ± 4·67 $l\,min^{-1}$, salbutamol 6·06 ± 4·34 $l\,min^{-1}$. Both bronchodilators produced statistically significantly ($P < 0·0001$) higher FEV_1 $AUC_{0-30\,min}$ than that observed with placebo (−0·32 ± 2·59 $l\,min^{-1}$) (Fig. 1).

The summary statistics for the secondary efficacy results are presented in Table 2. The increases in FEV_1, expressed as absolute values or changes from predose or percentage changes from predose, were very similar from 5 min to 3 h after the administration of formoterol 24 μg and that of salbutamol 400 μg (FEV_1 measurements over 3 h post-dose are shown in Fig. 2).

Bronchodilation became almost maximal by 30 min with both drugs, with the majority of benefit (80·0% of maximal effect with both drugs) being seen at 5 min.

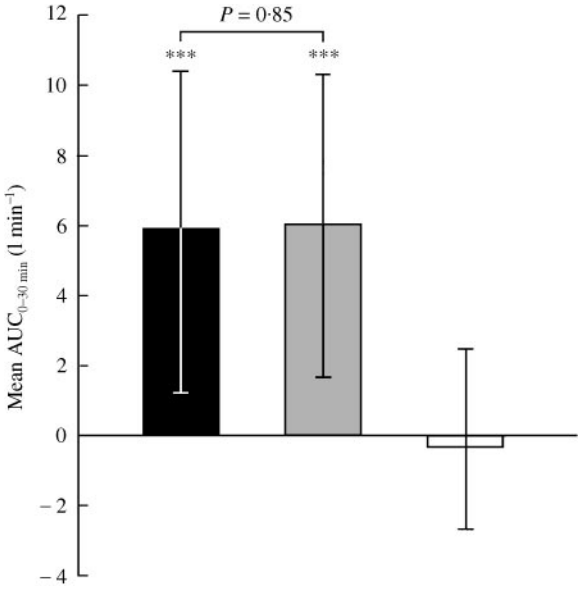

Fig. 1. FEV_1 AUC values for the first 3 h following inhalation of formoterol 24 μg (■), salbutamol 400 μg (■) or placebo (□). ITT population (n=24). Values are shown as mean ± SD for the ITT population. ***$P < 0·0001$ *vs.* placebo.

Safety

Two patients (8%) reported adverse events which were considered to be unrelated to the study drugs (one patient reported mild vertigo and another, acute bronchitis). No serious adverse events were reported and there were no discontinuations due to adverse events. No clinically relevant changes in vital signs were observed.

DISCUSSION

This study compared the onset of action of formoterol delivered via the Aerolizer™ dry powder inhaler, with

Table 2. Results of secondary efficacy parameters following single-dose inhalation of formoterol 24 μg, salbutamol 400 μg or placebo

Parameter	Formoterol	Salbutamol	Placebo	Formoterol *vs.* salbutamol contrast
AUC_{0-1h} (l min^{-1})	13·08 ± 8·79*	13·34 ± 9·38*	0·12 ± 5·09	P=0·88
AUC_{0-3h} (l min^{-1})	41·79 ± 27·36*	41·82 ± 27·88*	0·53 ± 16·88	P=0·99
Maximal change from predose FEV_1 (l)	0·34 ± 0·16*	0·35 ± 0·18*	0·11 ± 0·08	P=0·65
Maximal % change from predose FEV_1	26·0 ± 13·3*	27·0 ± 12·6*	8·0 ± 6·7	P=0·71
Maximal change from predose % predicted FEV_1 (l)	11·0 ± 5·3*	12·0 ± 5·2*	4·0 ± 2·7	P=0·78
Maximal change from predose FVC (l)	0·60 ± 0·33*	0·60 ± 0·41*	0·22 ± 0·22	P=0·96

All results are expressed as mean ± SD.
*Statistically significantly different from placebo ($P < 0·0001$).

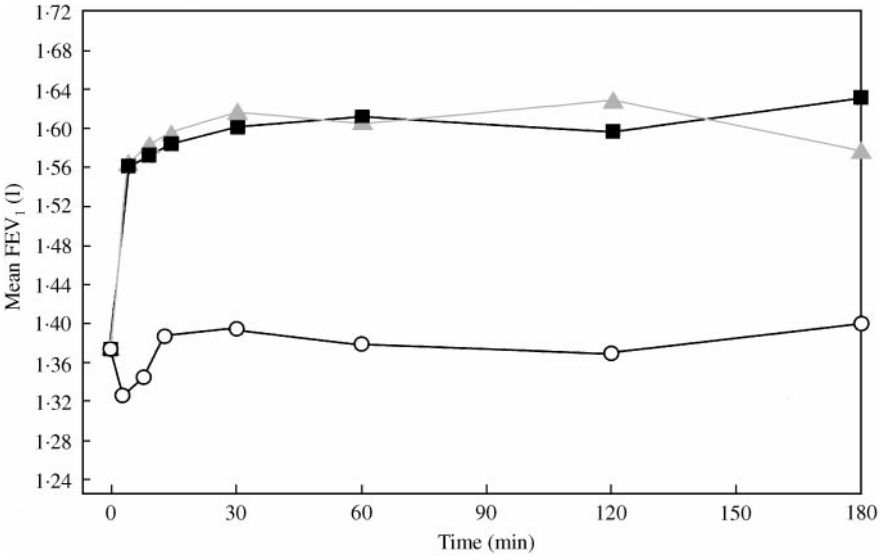

Fig. 2. Bronchodilator effect following single inhalation of formoterol 24 μg (■), salbutamol 400 μg (▲) or placebo (○): mean FEV_1 at each time-point in the first 3 h post-dose. ITT population (n=24).

that of salbutamol delivered via Diskhaler® dry powder inhaler, in patients with COPD.

The results confirmed the rapid onset of action of formoterol in COPD and showed that a single dose of formoterol 24 μg had a similar onset of action to salbutamol 400 μg observed within 5 min after administration. The increases in FEV_1, with both formoterol and salbutamol, showed little change from 5 min to 3 h after administration. The mean maximal changes observed with formoterol and salbutamol were very similar.

This single dose comparison provides results in patients with COPD that are similar to those obtained in asthmatics, where the bronchodilatory effects of formoterol are rapid and comparable with those of salbutamol (3). It also confirms the results of Dahl *et al.* (12), who showed formoterol to have an onset of action of less than 5 min in COPD, faster than that of ipratropium. Rapid onset of action is an important feature for bronchodilators in patients with COPD, since prompt symptom relief will give reassurance of effect and could be a key factor in patient compliance.

Patients selected for this study showed intermediate reversibility with salbutamol (5–15% over baseline) in order to exclude asthma categorically and to select patients open to improvement with β_2-agonist drugs. Therefore these patients may be representative of a potential population for reversibility testing with formoterol. Saligen derivatives, such as salbutamol, are only partial agonists; in contrast, formoterol is highly potent and displays much higher intrinsic activity, resulting in $>$80% relaxation even under induced tone (1). The rapid onset of action of formoterol and salbutamol is explained by the ability of these drugs to reach the β_2-adrenoceptor from the aqueous phase, but, unlike salbutamol,

formoterol is moderately lipophilic and consequently is retained in the membrane lipid bilayers and then continuously released, accounting for its long duration of action (1,14).

The results from this study indicate that formoterol may be considered for use in reversibility test in some patients with COPD where its rapid onset of action is similar to that of salbutamol but its ability to reverse airway obstruction may be greater and more predictable of the efficacy of a continuous treatment with formoterol.

CONCLUSIONS

This study showed that formoterol and salbutamol had similar rapid onset of bronchodilatory action in a group of 24 patients with COPD. Both drugs produced similar bronchodilation by 5 min, which was little different to the maximal bronchodilation. Formoterol is a unique β_2-agonist with a rapid onset of action and a long duration of action (1). These two features will ensure that the patients treated with formoterol experience rapid relief of symptoms together with long-term control of symptoms, thus making formoterol a very useful bronchodilator across the range of obstructive airways diseases.

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